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Manufacture of (all-rac)-alpha-Tocopherol

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Manufacture of (all-*rac*)- α -Tocopherol

The present invention is concerned with a novel process for the manufacture of (all-*rac*)- α -tocopherol by the acid-catalyzed reaction of trimethylhydroquinone (TMHQ) with isophytol (IP) or phytol (PH) in a solvent. As is known, (all-*rac*)- α -tocopherol (or as it has
5 mostly been denoted in the prior art, "d,l- α -tocopherol") is a diastereoisomeric mixture of 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyl-tridecyl)-6-chromanol (α -tocopherol), which is the most active and industrially most important member of the vitamin E group.

Many processes for the manufacture of d,l- α -tocopherol" (referred to as such in the literature reviewed hereinafter) by the reaction of TMHQ with IP or PH in the presence of
10 a catalyst or catalyst system and in a solvent or solvent system are described in the literature. These processes go back to the work of Karrer et al., Bergel et al. as well as Smith et al. [see Helv. Chim. Acta 21, 520 et seq. (1938), Nature 142, 36 et seq. (1938) and, respectively, Science 88, 37 et seq. (1938) and J. Am. Chem. Soc. 61, 2615 et seq. (1939)]. While Karrer et al. carried out the synthesis of d,l- α -tocopherol from TMHQ and phytol bromide
15 in the presence of anhydrous zinc chloride (ZnCl_2 ; a Lewis acid), not only Bergel et al. but also Smith et al. used TMHQ and PH as starting materials. In the following years mainly modifications, e.g. alternative solvents and Lewis acids, were developed. From the work of Karrer et al. there was developed in the year 1941 a technically interesting process for the manufacture of d,l- α -tocopherol which was based on the reaction of TMHQ with IP in the
20 presence of the catalyst system ZnCl_2 /hydrochloric acid (HCl) (US Patent 2,411,969). Later publications, e.g. Japanese Patent Publications (Kokai) 1985/054380, 1985/064977 and 1987/226979 [Chemical Abstracts (C.A.) 103, 123731s (1985), C.A. 103, 104799d (1985) and, respectively, C.A. 110, 39217r (1989)], describe this reaction in the presence of zinc and/or ZnCl_2 and a Brönsted (protonic) acid, such as a hydrohalic acid, e.g. HCl, trichloroacetic acid, acetic acid and the like, especially ZnCl_2 /HCl, as the catalyst system. Disad-
25 vantages of these and further published processes featuring ZnCl_2 in combination with a

Brönsted acid are the corrosive properties of the acids and the contamination of the waste water with zinc ions as a result of the large amount of ZnCl_2 required for the catalysis.

The manufacture of d,l- α -tocopherol by the reaction of TMHQ with phytyl chloride, PH or IP in the presence of boron trifluoride (BF_3) or its etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) is described
5 in German Patents 960,720 and 1,015,446 as well as in US Patent 3,444,213. However BF_3 too has corrosive properties.

Also, the reaction of TMHQ with IP or PH in the presence of a Lewis acid, e.g. ZnCl_2 , BF_3 or aluminium trichloride (AlCl_3), a strong acid, e.g. HCl , and an amine salt as the catalyst system is described in European Patent Publication (EP) 100,471. In an earlier
10 patent publication, DOS 2,606,830, the IP or PH is pretreated with ammonia or an amine before the reaction with TMHQ in the presence of ZnCl_2 and an acid is effected. In both cases corrosion problems occur.

A further interesting method for the manufacture of d,l- α -tocopherol from TMHQ and IP comprises using an isolated TMHQ- BF_3 or - AlCl_3 complex and a solvent mixture
15 featuring a nitro compound (DOS 1,909,164). This process avoids to a large extent the formation of undesired by-products because it involves mild reaction conditions. Thus, the use of such a solvent mixture is disadvantageous.

The manufacture of d,l- α -tocopherol by the reaction of TMHQ with IP using cation exchange resin complexes of metal ions (Zn^{2+} , Sn^{2+} and Sn^{4+}) is disclosed in Bull. Chem.
20 Soc. Japan 50, 2477-2478 (1977); amongst other disadvantages it gives the product in unsatisfactory yields.

The use of macroreticular ion exchangers, e.g. Amberlyst® 15, as the catalyst for the reaction of TMHQ with IP is described in US Patent 3,459,773. However, the d,l- α -tocopherol could not be obtained in the requisite purity.

25 EP 603,695 describes the manufacture of d,l- α -tocopherol in liquid or supercritical carbon dioxide by the reaction of TMHQ with IP or PH in the presence of acidic catalysts, such as ZnCl_2/HCl and ion exchangers. The reported yields are unsatisfactory.

The reaction in the presence of a catalyst system which consists of iron(II) chloride, metallic iron and HCl gas or aqueous solution is described in DOS 2,160,103 and US
30 Patent 3,789,086. The formation of less by-products is advantageous compared with the aforementioned process using ZnCl_2/HCl . However, corrosion problems and chloride contamination are equally disadvantageous.

An interesting alternative for the reaction of TMHQ with IP to d,l- α -tocopherol comprises using trifluoroacetic acid or its anhydride as the catalyst (EP 12824). Although in this process the avoidance of HCl is achieved, the catalyst is relatively expensive.

5 The use of the heteropoly acid 12-tungstophosphoric or 12-tungstosilicic acid as the catalyst for the reaction of TMHQ with IP was described for the first time in React. Kinet. Catal. Lett. 47(1), 59-64 (1992). d,l- α -Tocopherol could be obtained, using various solvents, in about 90% yield.

A further process described in the literature [EP 658,552; Bull. Chem. Soc. Japan 68, 3569-3571 (1995)] for the synthesis of d,l- α -tocopherol is based on the use of a various
10 lanthanide trifluoromethanesulphonates (triflates), e.g. scandium trifluoromethanesulphonate, as the catalyst for the reaction. With up to about 10% excess of IP this process gives yields up to 98%:

The use of ion-exchanged bentonite, montmorillonite or saponite through treatment with e.g. scandium chloride and other metal salts (yttrium, lanthanum, etc.) as the catalyst
15 for the reaction of TMHQ with IP or PH has as a disadvantage the need for a large amount of catalyst [EP 677,520; Bull. Chem. Soc. Japan 69, 137-139 (1996)].

According to the Examples of EP 694,541 the reaction of TMHQ with IP to α -tocopherol can be achieved in high yields and with a high product purity when such solvents as carbonate esters, fatty acid esters and certain mixed solvent systems are employed, the
20 exemplified catalysis being effected by ZnCl_2/HCl . Disadvantages in this process are, in addition to the contamination of the waste water by zinc ions, the usual large "catalyst amount" of ZnCl_2 used.

According to WO 97/28151 the acid-catalysed reaction of TMHQ with IP can be performed in a cyclic carbonate or α -lactone as the solvent. The preferred catalyst is a
25 mixture of orthoboric acid and oxalic, tartaric or citric acid, or boron trifluoride etherate.

WO 98/21197 describes the manufacture of d,l- α -tocopherol from TMHQ and IP using bis(trifluoromethylsulphonyl)imide or a metal salt thereof optionally together with a strong Brönsted acid, as catalyst in such types of aprotic solvents as aliphatic and cyclic ketones or esters, and aromatic hydrocarbons.

30 Using the same kind of bis(trifluoromethylsulphonyl)imide catalyst it has been shown in EP 1,000,940 that the d,l- α -tocopherol manufacturing process can also be realized in supercritical carbon dioxide or nitrous oxide as the solvent.

From the foregoing review it is evident that most of the previously known processes have considerable disadvantages. Thus, corrosion problems occur in all processes in which such acid catalysts as boron trifluoride are used. Toxicity problems with the boron trifluoride adducts also occur, and when iron or zinc is used there is a contamination of the waste water with the metal ions which is today no longer acceptable. In some processes the formation of undesired by-products, e.g. phytoltoluenes, chlorophytols, and products of the dehydration of IP or PH, i.e. so-called phytadienes, is an especially serious problem: the selectivity of the reaction is unsatisfactory. In most cases the yields are unsatisfactory.

The object of the present invention is to provide a process for the manufacture of (all-*rac*)- α -tocopherol by the reaction of trimethylhydroquinone with isophytol or phytol in the presence of a catalyst and in a solvent which does not have the disadvantages of previously known procedures. In this respect, it is necessary that the catalyst used has no, or at least a much reduced, corrosive action, is non-toxic, does not contaminate the environment, e.g. with chlorinated by-products or heavy metal ions, and catalyzes the desired reaction as selectively as possible, with as little as possible co-production of such by-products as phytadienes, and in high yields. Furthermore, the catalyst should display its activity in small, really catalytic, amounts and should be readily separable and re-usable several times.

This object of the present invention is achieved by carrying out the reaction of trimethylhydroquinone with isophytol or phytol in the presence of $\text{CH}(\text{SO}_3\text{H})_3$ as the catalyst in an organic solvent.

Accordingly, the present invention is concerned with a process for the manufacture of (all-*rac*)- α -tocopherol by the acid-catalyzed reaction of trimethylhydroquinone with isophytol or phytol, which process is characterized by carrying out the reaction in the presence of $\text{CH}(\text{SO}_3\text{H})_3$ as the catalyst in an organic solvent.

The compound $\text{CH}(\text{SO}_3\text{H})_3$ used as the catalyst in the process of the present invention is a known compound and can be prepared from acetone or acetanilide in oleum, see, e.g. J.Prakt.Chem. 1994, 336, 373; Z. Naturforsch. 1996, 51b, 1691; J.Chem.Soc.Dalton 1980, 149; and Rec.Trav.Chim. Pays-Bas 1930, 49, 1107.

Solvents which can be used in the process of the present invention are all types of Solvents for Friedel-Crafts reactions, preferably polar aprotic organic solvents, e.g., alkylene carbonates, such as ethylene carbonate, propylene carbonate or 1,2-butylenecarbonate, esters such as butyl acetate, ketones such as diethyl ketone, lactones such as γ -butyrolactone, and mixtures of these solvents. Most preferred are two-phase solvent systems, particularly ethylene carbonate or propylene carbonate or 1,2-butylenecarbonate, and hexane, heptane and octane, especially ethylene carbonate and heptane,

propylene carbonate and heptane, and ethylene/propylene carbonate and heptane, wherein the ratio of ethylene or propylene carbonate to hexane, heptane or octane is in the range of about 5:1 to 1:10, preferably about 1:1.125 to 2:1 by volume. When mixture comprising ethylene carbonate and propylene carbonate are used the ratio of ethylene carbonate to propylene carbonate is suitably in the range of about 1.0 : 100 to 100 : 1, preferably 1.0 : 10 to 10 : 1, special preferred 1:1.

The process is conveniently effected at temperatures from about 353K to about 433K, preferably from about 363K to about 423K, especially from about 373K to about 415K.

Furthermore, the molar ratio of trimethylhydroquinone to isophytol or phytol is conveniently about 1.25 : 1 to about 2.2 : 1, preferably about 1.5 : 1 to about 2 : 1.

The amount of catalyst, $\text{CH}(\text{SO}_3\text{H})_3$, is such that the molar ratio of the catalyst to the educt (trimethylhydroquinone or isophytol/phytol) which is in the lesser molar amount, generally the isophytol or phytol, is conveniently about 0.01 mole % to about 0.1 mole %, preferably about 0.0125 mole % to about 0.08 mole %.

Conveniently about 0.5 - 2 ml, preferably about 0.75 - 1.25 ml, most preferably about 0.9-1.1 ml, of a polar solvent are used per mmol of trimethylhydroquinone.

If the process is carried out with a biphasic solvent system, especially one consisting of a polar solvent, e.g., and as preferred, a cyclic carbonate such as ethylene carbonate, propylene carbonate, 1,2-butylene carbonate or a mixture of two or all three of these cyclic carbonates, and a non-polar solvent, e.g. an aliphatic hydrocarbon such as hexane, heptane or octane, then the volume ratio of the non-polar solvent to the polar solvent is conveniently in the range from about 1 : 3 to about 5 : 1, preferably from about 1 : 1.25 to about 2 : 1.

Moreover, the process is conveniently carried out under an inert gas atmosphere, preferably gaseous nitrogen or argon.

The actual reaction generally lasts for about 0.5 to about 2.5 hours, preferably about 0.75 to 1.5 hours.

The process in accordance with the invention can be carried out batchwise or continuously, and in general operationally in a very simple manner, for example by adding isophytol or phytol, as such or in solution, portionwise to a mixture of the catalyst, the trimethylhydroquinone and the solvent. The catalyst can be added in solid form or, preferably, as an aqueous solution. The rate at which the isophytol or phytol is added is

not critical. Conveniently, isophytol or phytol, preferably as such, is added continuously over a period from about 5 minutes to about 1 hour, preferably from about 10 to 30 minutes. After completion of the isophytol/phytol addition and an appropriate subsequent reaction period the working-up can be effected by procedures conventionally used in organic chemistry.

If desired, the obtained (all-*rac*)- α -tocopherol can be converted into its acetate, succinate, poly(oxyethylene)succinate, nicotinate and further known application forms by standard procedures [see, for example, the 5th Edition of Ullmann's Encyclopedia of Industrial Chemistry, Vol. A 27, pages 484-485 (VCH Verlagsgesellschaft mbH, D-69451 Weinheim, 1996)].

The process in accordance with the invention enables the catalyst used to be separated readily and to be reused several times.

Advantages in the use of the catalyst in the process in accordance with the invention are, in addition to high yields of (all-*rac*)- α -tocopherol, the avoidance of corrosion, the avoidance of waste water contamination with heavy metal ions, the high selectivity as well as the enabled ready isolation of the produced (all-*rac*)- α -tocopherol from the mixture after reaction.

The process in accordance with the invention is illustrated by the following Example:

Example 1

7.55 g (50 mmol) trimethylhydroquinone (purity 99.7 %), 40 g ethylene carbonate (or propylene carbonate) and 50 ml heptane were introduced into a 200-ml four-necked flask equipped with a reflux condenser, a water separator, a mechanical stirrer and argon gasification means and heated to reflux temperature (bath temp. 140 °C) under argon atmosphere. After the addition of $\text{CH}(\text{SO}_3\text{H})_3$ as an aqueous solution (for 0.05 mol% : 4.23 mg = 391 μl), 12.026 ml (33 mmol) of isophytol were added at a rate of 0.6 ml/minute. The heptane was distilled off and the mixture was heated to 125-130 °C for 30 min, then cooled to 80 °C. 50 ml of heptane were added to the ethylene carbonate phase. The reaction mixture was stirred for a further 10 min. at 50 °C. The heptane layer was separated and evaporated under reduced pressure to give (all-*rac*)- α -tocopherol as a viscous oil in a yield shown in Tables 1 and 2.

Table 1

Amount of catalyst (mole % relative to IP)	Solvent	Yield (%)
0.16	EC + heptane	98.2
0.056	EC + heptane	97.2
0.05	EC + heptane	95.3
0.05	PC + heptane	91.2

EC = ethylene carbonate; PC = propylene carbonate

Table 2

Ratio EC/heptane (g/ml)	Addition of IP during (min)	Yield (%)
10/80	20	99.2
10/80	60	97.7
20/70	20	96.1
10/50	20	92.4
20/50	20	94.5
40/50	20	95.3

EC = ethylene carbonate; PC = propylene carbonate; IP = Isophytol

5 Amount of catalyst : 0.05 mol% based on IP; ratio TMHQ : IP = 1.5:1.

If desired, the crude product can be converted into its acetate by standard procedures.

What is claimed is:

1. A process for the manufacture of (all-*rac*)- α -tocopherol by the acid-catalyzed reaction of trimethylhydroquinone with isophytol or phytol, which process is characterized by carrying out the reaction in the presence of $\text{CH}(\text{SO}_3\text{H})_3$ as the catalyst in an organic solvent.
2. A process according to claim 1, wherein the solvent is a polar aprotic solvent or solvent mixture.
3. A process according to claim 2, wherein the solvent is a mixture of one or more alkylene carbonates and hexane, or heptane or octane.
4. A process according to claim 3, wherein the solvent is a mixture of ethylene carbonate and hexane or heptane or octane.
5. A process according to claim 4, wherein the solvent is a mixture of ethylene carbonate and heptane.
6. A process according to claim 3, wherein the solvent is a mixture of propylene carbonate and hexane, heptane or octane.
7. A process according to claim 3, wherein the solvent is a mixture of propylene carbonate and heptane.
8. A process according to claim 7, wherein the solvent is a mixture of ethylene carbonate and propylene carbonate with hexane, heptane or octane.
9. A process according to claim 8, wherein the solvent is a mixture of ethylene carbonate, propylene carbonate and heptane.
10. A process according to claim 4 or 6, wherein the ratio of ethylene carbonate to hexane, heptane or octane is in the range of about 5:1 to 1:10, preferably about 1:1.125 to 2:1 by volume.
11. A process according to claim 6 or 7, wherein the ratio of propylene carbonate to hexane, heptane or octane is in the range of about 5:1 to 1:10, preferably about 1:1.125 to 2:1 by volume.
12. A process according to claim 8 or 9, wherein the ratio of ethylene carbonate to propylene carbonate is in the range of about 1.0 : 100 to 100 : 1. preferably 1.0 : 10 to 10 : 1, special preferred 1:1.

13. A process according to claim 8 or 9, wherein the ratio of ethylene carbonate/propylene carbonate to hexane, heptane or octane is in the range of about 5:1 to 1:10, preferably about 1:1.125 to 2:1 by volume.

5 14. A process according to any one of claims 1 to 13, wherein the molar ratio of trimethylhydroquinone to isophytol or phytol present in the reaction mixture is about 1.25 : 1 to about 2.2 : 1, preferably about 1.5 : 1 to about 2 : 1.

15. A process according to any one of claims 1 to 14, wherein the relative amount of the catalyst to the amount of trimethylhydroquinone or isophytol/phytol, whichever is in the
10 lesser molar amount, is about 0.01 mole % to about 0.1 mole %, preferably about 0.0125 mole % to about 0.08 mole %.

16. A process according to any one of claims 1 to 15, wherein the reaction is effected at temperatures from about 353 K to about 433 K, preferably from about 363 K to about 423 K, especially from about 373 K to about 415 K.

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